REMARKS

Claims 1, 13-23, 25-33 and 37-52 are pending in the present application.

This application was filed August 18, 2000 and therefore has been pending *over* five years. The instant Office Action is the *seventh* Office Action (including the Advisory Action mailed November 21, 2002) mailed by the USPTO in the file history. MPEP 707.02[1] states that any application that has been pending five years should be carefully studied by the supervisory patent examiner and every effort should be made to terminate its prosecution. Pursuant to MPEP 707.02, Applicants request that the Supervisory examiner, James Housel, review this application with a view to finally concluding its prosecution. MPEP 707.02 states that to accomplish this result, the application is to be considered "special" by the examiner. Applicants request that the examiner consider this application as "special" due to the length of its pendency and the number of Office Actions mailed.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1, 13-23, 25-30, 32, 33 and 37-42 stand rejected under 35 U.S.C. 112, first paragraph, because, allegedly the specification, while being enabling for using an ISS molecule comprising SEQ ID NO: 1, does not reasonably provide enablement for IS sequences that are shorter or do not conform to the enabled motif.

Applicants traverse this rejection of claims. Applicants submit that the specification enables the claimed invention across the full scope. The Examiner has not provided adequate evidence to support a *prima facie* case of non-enablement. Furthermore, Applicants point out that MPEP 707.02 states that the shortest path to final disposition of an application is by finding the best references on the first search and carefully applying them. The instant Section 112, first paragraph enablement rejection based on Fearon et al. and directed to ISS (recited in the claims *as filed*) was not applied until March 9, 2004, the *fifth* Office Action in this prosecution history.

[1] Applications up for third action and 5-year applications.

In the March 9, 2004 Office Action at page 4, the Examiner states with respect to Fearon et al.: "As evidenced by the teachings of Fearon et al., a polynucleotide merely containing the short sequences recited are not immunostimulatory. That is the basis of this enablement rejection". To comply with the requirements of Section 112, first paragraph, a specification must adequately teach how to make and how to use a claimed invention, throughout its scope without undue experimentation. The fact that Fearon et al. may report on sequences that are not immunostimulatory does not in itself support a finding of non-enablement of the pending claims. In fact, Fearon et al. at page 2114 in the Introduction acknowledges that: "The *in vivo* activity of ISS ODN as therapeutics in models of asthma and cancer and as vaccine adjuvants has been demonstrated in mice and primates".

The specification teaches how to make and use the claimed invention without undue experimentation. Claim 1 recites a method of modulating an immune response to a second antigen in an individual, comprising co-administering to the individual (i)a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and (ii)a second antigen wherein the polynucleotide comprises an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'-cytosine, guanine-3', wherein the complex and the second antigen are administered at the same site in the individual and wherein the complex is administered in an amount sufficient to modulate an immune response in the individual to the second antigen. Claim 37 recites a composition comprising (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and (ii) a second antigen,

wherein the polynucleotide comprises an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'-cytosine, guanine-3', and wherein the first antigen is a viral conserved polypeptide and the second antigen is a viral variable polypeptide. Claim 40 recites a composition comprising (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and (ii) a second antigen, wherein the polynucleotide comprises an immunostimulatory sequence (ISS), wherein the ISS comprises the sequence 5'-cytosine, guanine-3', and wherein the first antigen is an allergen.

Applicants respectfully submit that the specification provides all the information required for one of skill in the art to make and use the claimed invention to modulate the immune response to the second antigen as claimed. The specification teaches the requirements for the ISS and the immunomodulatory polynucleotide of the complex and provides methods by which ISS can be made and evaluated for immunomodulatory activity. See, for example, page 15, line 30, to page 21, line 17. The specification describes antigens and how to make the polynucleotide-antigen complexes for use in the invention. See, for example, page 21, line 20, to page 32, line 19. The specification provides guidance for the administration and formulations for administration of the claimed compositions. See, for example, page 39, line 30, to page 47, line 8. Finally, the specification provides methods to assess the modulation of the immune response as claimed. Such disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

The Examiner alleges at page 3 of the instant Office Action that Fearon et al. clearly show that just because an ISS molecule has two CpG motifs present, the determination of whether it possesses immunomodulatory effects cannot be determined without experimentation. A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants respectfully submit that varying the nucleic acid sequence of oligonucleotides and testing the oligonucleotides for immunostimulatory activity are well within the bounds of routine experimentation by one of skill in the art. The Examiner alleges at page 3 of the Office Action that a sequence in Fearon et al. is demonstrated to be non-immunogenic when in a complexed and non-complexed form. The Examiner further alleges that the skilled artisan would be unable to predict which characteristics are required for a sequence to be immunostimulatory. If true, this in itself does not support a finding of non-enablement because some degree of unpredictability is permitted, depending upon the level of guidance provided in the specification and knowledge in the art. The specification provides all the information required for one of skill in the art to make and use the claimed invention. The Examiner states that in the instant application, the specification only exemplifies the immunomodulatory capabilities of SEQ ID NO:1. This in itself does not support a

finding of non-enablement. One of skill in the art given the teachings of the specification would be able to practice other permutations of the invention without resorting to undue experimentation.

Applicants amendment mailed December 22, 2004 states that the USPTO has issued claims directed to methods of treating a mammal, a subject or an individual through administering an immunostimulatory or immunomodulatory polynucleotide comprising an ISS, wherein the ISS comprises the sequence 5'-C, G-3'.[2] The Examiner states at page 4 of the instant Office Action that these patents are not relevant to the instant application since the method of treatment is unrelated and the claimed compositions do not resemble the one instantly claimed. Applicants assert that the relevance of these patents is that they each contain claims that recite the sequence 5'-C, G-3' and were found by the USPTO to be in compliance with Section 112, first paragraph.

Thus, Applicants respectfully submit that the pending claims are in compliance with the enablement requirements and a *prima facie* case of non-enablement has not been established.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §103(a)

I. Claims 1, 13, 14, 17, 20-23, 25-33, 37 and 40-42 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Shwartz et al. (WO 98/55495, "Schwartz") or Carson et al. (WO 98/16247, "Carson"), as further evidenced by Horner et al. (Cellular Immunology. November, 1998; 190: 77-82) or Chu et al. (Journal of Experimental Medicine. 1997; 186 (10): 1623-1631) for reasons of record.

II. Claims 15 and 38 are rejected under Section 103 as allegedly unpatentable over Schwartz et al. or Carson et al. as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 11, 13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Lee et al.

[2] See, for example, U.S. Pat. Nos. 6,613,751, 6,552,006, 6,534,062 and 6,498,148, previously submitted.

III. Claims 16 and 39 are rejected under Section 103 as allegedlyunpatentable over Schwartz et al. or Carson et al. as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 11, 13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Durali et al.

IV. Claims 18 and 19 are rejected under Section 103 as unpatentable over Schwartz et al. or Carson et al. as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 11, 13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Anderson et al.

Applicants traverse this rejection of claims. Applicants do not agree or concede that a *prima facie* case of obviousness has been established and submit that the invention is non-obvious in view of the cited references. In order to establish a *prima facie* case of obviousness, there has to be, *inter alia*, some motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine reference teachings. Applicant submits that there is no motivation to combine references and, even if combined, the combination of references does not provide a reasonable expectation of successfully arriving at the claimed invention and does not teach or suggest the claimed invention.

In making this rejection, the Examiner states at page 6 of the instant Office Action that the instant claims are drawn to a method with two components: (i) an ISS-antigen complex[3] and (ii) an un-complexed second antigen. The Examiner then points to pages of Schwartz that are alleged to disclose either component i. or component ii and alleges at page 6 that "Schwartz et al. do suggest the instant composition claimed". First, this statement of the Examiner in the instant Office Action is contradictory to the statement the Examiner made in the Office Action mailed April 23, 2002, at page 3, where it is stated, " Schwartz does not explicitly teach administering a second antigen with the composition." In fact, Schwartz at page 12, lines 29-31 and page 14, lines 8-14, cited by the Examiner, have no disclosure or suggestion of methods of modulating an immune response to a *second antigen* comprising co-administering i. and ii. as recited in claim 1 or of the compositions recited in the instant claims. In determining obviousness, Section 103 expressly requires considering the claimed invention *as a whole*. The properties and advantages of the invention are

[3] Claims 1, 37, and 40 recite that the only polynucleotide is covalently conjugated to a first antigen.

part of the invention as a whole. As demonstrated in the specification, the observed benefit of the claimed methods, i.e., co-administration of a complex comprising an immunomodulatory polynucleotide (that comprises an ISS) covalently conjugated to a first antigen complex and a second antigen, is the modulation of the immune response to the *second antigen*. By isolating individual components of the claimed invention and selecting from among a variety of disclosures in Schwartz (or Carson) to try and piece together the claimed invention, the Examiner is improperly disregarding the "as a whole' statutory mandate and the Section 103 rejection must fail as a matter of law.

With respect to Carson, in the Office Action mailed April 23, 2002 at page 5, the Examiner states that while Carson does not explicitly teach administering a second antigen, administering a second antigen would be an obvious variation to their teachings. In the Office Action mailed November 21, 2002 at page 4[4], the Examiner acknowledges that Carson does not explicitly teach administering a second antigen, and states "the reference suggests doing so without unexpected results". The instant specification demonstrates the benefit of the claimed invention, i.e. methods, and compositions for use in methods, that modulate the immune response to the *second antigen that is administered*. Carson does not teach administering a second antigen much less suggest the advantages of the claimed invention, i.e., modulating the immune response to the *second antigen*. There are no suggestions in Carson (or Schwartz) taken alone or together with the secondary references that would suggest the benefits of the claimed invention.

Without an understanding of this benefit, one skilled in the art would have no motivation to produce the claimed invention. Neither Schwartz nor Carson teach or suggest that co-administration of an ISS-first antigen complex and a second antigen results in the modulation of the immune response to the *second antigen*. Neither Schwartz nor Carson teach or suggest the claimed compositions. Thus, the references provide *no motivation* for modifying the teaching therein to arrive at the claimed invention. Nothing in Schwartz or Carson provides motivation to the skilled artisan to administer an ISS-first antigen conjugate complex in an amount sufficient to modulate an

[4] and the Office Action mailed June 2, 2003 at page 12.

immune response to a co-administered second antigen. Even if the references were properly combined, one of skill would not arrive at the presently claimed invention.

For reasons already of record, none of the secondary references provide what is missing from the primary references, Schwartz or Carson. Horner et al. and Chu et al. are cited by the Examiner as allegedly teaching a Th1 response is induced against an antigen co-administered with an ISS. See Office Action March 9, 2004, page 9. Lee et al. is cited by the Examiner as allegedly teaching that the "influenza nucleocapsid protein is the least affected by antibody induced antigenic drift".[5] Durali et al. is cited by the Examiner as teaching that the gag protein is capable of cross-reactivity in different patients infected with different clades of HIV.[6] Anderson et al. is cited by the Examiner as teaching diphtheria toxins.[7] None of the secondary references teach or suggest modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen. None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen. None of the references, either alone or in combination, describes or suggests the composition as claimed. Nothing in the references, or in the art, suggests that the benefit of conjugation to an ISS would be extended to the second antigen. Thus, the cited references do not provide an expectation of success of the claimed invention, i.e., modulating an immune response to a second antigen.

In sum, Applicants respectfully submit that a *prima facie* case of obviousness has not been made. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

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[5] See Office Action mailed March 9, 2004 at page 10.
[6] See Office Action mailed March 9, 2004 at page 11.
[7] See Office Action mailed March 9, 2004 at page 12.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882000800. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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